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Prognostic significance of interim ^{18}F-FDG PET/CT SUV reduction associated with Ki67 in patients with diffuse large B-cell lymphoma

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To detect the prognostic significance of interim ^{18}F-FDG PET/CT SUV (standard uptake value) reduction (ΔSUV$_{max}$) associated with Ki67 in patients with diffuse large B cell lymphoma (DLBCL). 47 DLBCL patients underwent PET/CT before initiation and after 2–4 cycles of chemotherapy were included. The SUV$_{max}$ of the dominant lesions were calculated. Ki67 positive indices were provided by enzyme-labeled immunohistochemistry. SPSS17.0 was used for statistical analysis. ΔSUV$_{max}$ of different groups were compared by t test. Receiver-operator characteristic analysis was performed to determine the optimal cutoff values. Kaplan-Meier analyses of PFS (Progression-free survival) were compared using log-rank test. The average of ΔSUV$_{max}$ and ΔSUV$_{max}$% were 11.53 and 69.10%, respectively. The optimal cutoff values of ΔSUV$_{max}$ and ΔSUV$_{max}$% were 11.45 and 82.92%, respectively. Higher ΔSUV$_{max}$ and ΔSUV$_{max}$% indicated longer PFS ($p < 0.001$). The optimal cutoff value of Ki67 was 55%. Ki67$\geq$55% was revealed to be an indicator of shorter PFS ($p = 0.019$). Either ΔSUV$_{max}\leq$11.45 or Ki67$>$55% was defined as an indicator to poor outcome and scored 1 point. The PFS rate was 100% in patients scored 0 point, yet 0% in patients scored 2 points. PFS tended to be shorter along with the score getting higher ($p = 0.006$). ΔSUV$_{max}$ and Ki67 positive index were both of significance in DLBCL prognosis. The prognostic value may be confirmed when ΔSUV$_{max}$ was accordant with Ki67.

Keywords: Diffuse large B cell lymphoma, Standard uptake value, Ki67, Prognosis

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I. INTRODUCTION

Diffuse Large B-Cell Lymphoma (DLBCL) is a common lymphoid neoplasm in adults, and is an aggressive Non-Hodgkin Lymphoma (NHL). Thanks to the development of chemotherapeutics, especially the invention of Rituximab, and the progression of autologous stem cell transplantation, DLBCL patients now can maintain remission for a relatively long period.

However, problems such as refractory lymphoma and tumor relapse still make trouble in the management of DLBCL. Also, acute and long-term side effects caused by chemotherapeutic agents play a role in patients' death. To solve these problems, risk-adapted therapy is necessary, the basis of which is assessing prognosis as early as possible.

^{18}F-FDG PET/CT is a metabolic imaging technique reflecting glucose metabolism. The roles of PET/CT in staging, response assessment, prognosis and follow-up of DLBCL have been demonstrated and brought into guidelines of NHL for years [1], and FDG PET after the therapy proved to be of determinate value for prognosis. However, to do early assessment, PET/CT scans should be performed at earlier stages of the disease treatment, such as after 2 or 4 cycles (interim) of chemotherapy.

Effects were made in detecting an appropriate criterion for interim PET/CT scan. Yet the visual analysis was regarded as not reliable enough by several groups [2, 3], and the semi-quantitative analysis based on standard uptake value (SUV) was thought to be capable of improving the prognostic accuracy [4], especially the SUV reduction analysis [2, 5].

Ki67 is a nuclear antigen expressing in cell generation cycle, and is absent in resting phase cells. It is a dependable parameter for measuring tumor cell proliferation index. High Ki67 positive index was demonstrated to be an indicator of poor outcome [6–9].

As SUV reduction reflects the changes of glucose metabolism after therapy, and Ki67 reports tumor cell proliferation index, an integration of them includes information of both aspects. This study is aimed at detecting the prognostic significance of interim ^{18}F-FDG PET/CT SUV reduction associated with Ki67 in DLBCL patients.

II. MATERIALS AND METHODS

A. Patients

Forty-seven pathologically confirmed DLBCL patients who underwent PET/CT scan from July 2007 to June 2011 were included. Any patients of past tumor history were excluded. All patients accepted first-line chemotherapeutic strategy (CHOP, R-CHOP, or CHOPE) after diagnosis. The follow-up duration ranged from 14–52 months (median 34 months), and the follow-up rate was 95.7% (45/47) . The clinical characteristics of the patients are summarized in Table 1.

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TABLE 1. Patient Characteristics ($n = 47$)

Characteristic	Total
Median age, y (range)	50 (18–83)
Sex: Male/Female	29/18
Ann Arbor stage, no. (%)	
I-III	18 (38.3)
IV	29 (61.7)
IPI[a] score, no. (%)	
Low-High/Intermediate	32 (68.1)
High	15 (31.9)

[a] IPI= International Prognostic Index

B. ^{18}F-FDG PET/CT

All the patients were scanned on Discovery STE16 PET/CT (GE). Radiochemical purity ($> 95\%$) of the FDG and all other specifications, met the quality requirements of radiopharmaceuticals.

The patients underwent PET/CT before (initial) and after 2–4 cycles (interim) of chemotherapy. The patients fasted for 6 h, and their blood glucose was lower than 7.8 mmol/L. The data acquisitions lasted 50–60 min after intravenous injection with 0.12–0.15 mCi/kg of ^{18}F-FDG uptake, which were consisted of 5–7 bed shifts, covering from the upper thigh to the top of the skull. For each bed position except the skull, a 3 min emission scan was acquired, and for the bed position of skull, the duration was 5 min. The acquisition featured a low dose transmission CT scan (100 kV, 40 mAs, slice thickness: 5 mm).

C. SUV-based assessment of ^{18}F-FDG uptake

For each PET dataset, the tumor with the most intensive ^{18}F-FDG uptake of all foci was carefully identified as the dominant lesion. Regions of interest (ROIs) were drawn around the dominant lesions, and the $\mathrm{SUV_{max}}$ were calculated by a computer code on a Xeleris workstation and normalized through body surface area, using Eqs. (1) and (2):

$$\mathrm{SUV} = \frac{\text{Tissue activity (kBq/ml)}}{\text{Injectied activity (MBq/ml)} \cdot \mathrm{BSA}} \tag{1}$$

$$\begin{aligned}\text{BSA (Body Surface Area)} =& 0.007184 \times \text{Height}^{0.725} \\ & \times \text{Weight}^{0.425}\end{aligned} \tag{2}$$

In patients whose lesions disappeared totally after 2–4 cycles of chemotherapy, regions of interest were drawn around the same area in interim PET images as in initial ones. $\Delta\mathrm{SUV_{max}}$ and $\Delta\mathrm{SUV_{max}}\%$ were calculated as follows:

$$\Delta\mathrm{SUV_{max}} = \mathrm{SUV_{max}}(\text{initial}) - \mathrm{SUV_{max}}(\text{interim}) \tag{3}$$

$$\Delta\mathrm{SUV_{max}}\% = \frac{\mathrm{SUV_{max}}(\text{initial}) - \mathrm{SUV_{max}}(\text{interim})}{\mathrm{SUV_{max}}(\text{initial})} \tag{4}$$

D. Ki67 positive index

Ki67 positive indices were provided by enzyme-labeled immunohistochemistry. The negative control was PBS, and positive control was given positive section. "Positive result" was defined as cell nuclei presenting to be stained for the antigen. For each section, 5 high-power fields were chosen, 200 tumor cells were counted randomly in each field, and the ratio of Ki67 positive tumor cells to 1000 tumor cells was computed.

E. Statistical analysis

SPSS17.0 was used for statistical analysis. PFS was chosen as the endpoint, which was defined as the interval from the date of enrollment to the first evidence of progression or relapse or to the date of death from any cause. The data were censored if the patients were alive or free from progression or relapse at the last follow-up. Independent sample t test was used to compare the $\mathrm{SUV_{max}}$ reduction in patients of different stages, IPIs and follow-up results. Receiver-operator characteristic (ROC) analysis was performed to determine the optimal cutoff values of $\Delta\mathrm{SUV_{max}}$, $\Delta\mathrm{SUV_{max}}\%$ and Ki67 positive indices for predicting patients' outcome (progression or death vs. free from progression). Survival curves according to SUV-based assessment and Ki67, and the integration of both the variants, were obtained using Kaplan-Meier analysis and were compared using the log-rank test. Significance was obtained when the 2-sided p value was less than 0.05.

III. RESULTS

A. Patients outcome

During the follow up, 19 (42.2%) of the 45 cases were free from progression. The remaining 26 cases were found to take progression with a median delay of 10.0 months.

B. Prognostic significance of $\Delta\mathrm{SUV_{max}}$ and $\Delta\mathrm{SUV_{max}}\%$

Before therapy, the $\mathrm{SUV_{max}}$ was 18.16 ± 6.54, and it decreased to 5.20 ± 4.89 after 2–4 cycles of chemotherapy. The averaged $\Delta\mathrm{SUV_{max}}$ and $\Delta\mathrm{SUV_{max}}\%$ were 11.53 ± 5.53 and $(69.10 \pm 27.90)\,\%$, respectively. The $\Delta\mathrm{SUV_{max}}$ and $\Delta\mathrm{SUV_{max}}\%$ of different groups are given in Table 2. The patients suffered from high IPI and progression during the follow-up showed significantly low $\Delta\mathrm{SUV_{max}}$ and $\Delta\mathrm{SUV_{max}}\%$ ($0.001 \leq p \leq 0.008$). The $\Delta\mathrm{SUV_{max}}\%$ was also significantly low in stage IV patients. The $\Delta\mathrm{SUV_{max}}$ tended to be low in stage IV patients,though the difference was no significant.

According to ROC analysis, the optimal cutoff values of $\Delta\mathrm{SUV_{max}}$ and $\Delta\mathrm{SUV_{max}}\%$ were 11.45 and 82.92% for PFS prediction, respectively (Fig. 1). The accuracies were

TABLE 2. ΔSUV_{max} and $\Delta SUV_{max}\%$ of different groups

Group		n	ΔSUV_{max}	p	$\Delta SUV_{max}\%$	p
Stage	I-III	18	13.49±5.21	0.055	(80.73±11.47)%	0.007
	IV	29	10.31±5.46		(61.89±32.19)%	
IPI	Low-High/Intermediate	32	12.96±5.05	0.008	(79.43±17.21)%	0.003
	High	15	8.47±5.43		(47.07±33.66)%	
Outcome	Free from progression	19	15.06±4.38	<0.001	(85.26±6.50)%	< 0.001
	With progression	26	8.79±4.86		(56.50±31.87)%	

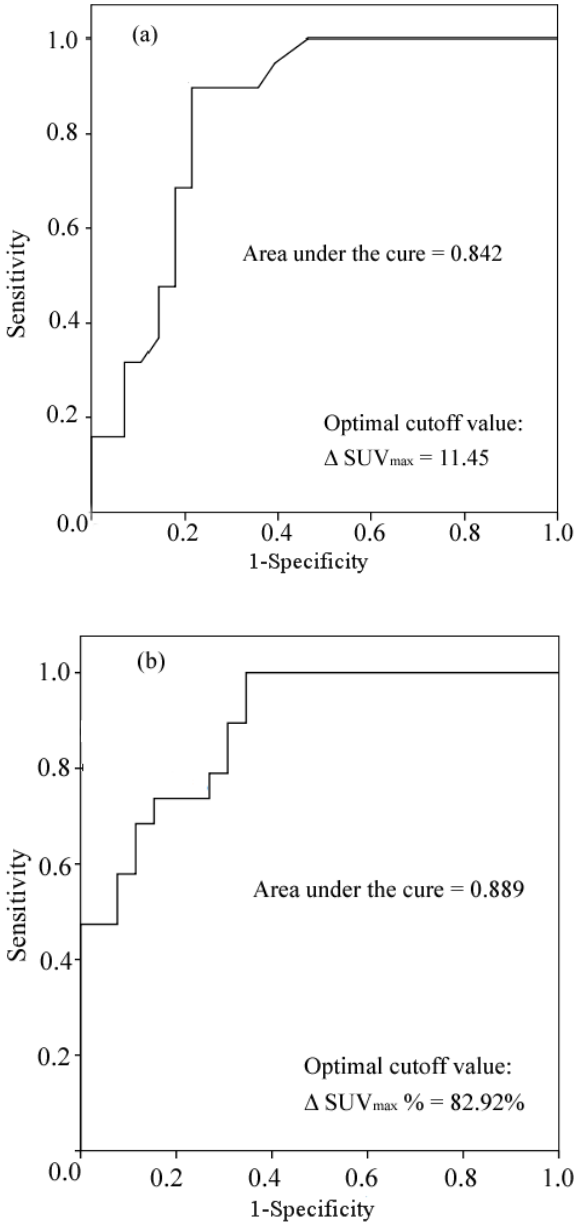

Fig. 1. ROC analysis of ΔSUV_{max} (a) and $\Delta SUV_{max}\%$ (b) for PFS prediction.

TABLE 3. Predictive value based on ΔSUV_{max} and $\Delta SUV_{max}\%$

Group	Total n.	Events	2-y PFS rate (%)	PPV (%)	NPV (%)
ΔSUV_{max}>11.45	22	5	77.3	77.3	/
$\Delta SUV_{max}\leq$11.45	23	21	8.7	/	91.3
$\Delta SUV_{max}\%$ >82.92%	18	4	77.8	77.8	/
$\Delta SUV_{max}\%$ ≤82.92%	27	22	18.5	/	81.5

TABLE 4. PFS estimates

Run Time(s)	Total n	PFS (months)		
		Average	SD	95% CI
All Patients	45	24.9	3.1	18.9–30.9
ΔSUV_{max} > 11.45	22	40.0	4.0	32.2–47.7
$\Delta SUV_{max}\leq$11.45	23	11.7	1.1	9.7–14.1
$\Delta SUV_{max}\%$ > 82.92%	18	39.0	4.9	29.5–48.6
$\Delta SUV_{max}\%$ ≤82.92%	27	14.1	1.7	10.8–17.5
Ki67 ≤55%	9	18.9	1.4	16.2–21.6
Ki67> 55%	16	17.7	3.7	9.9–24.3

84.4% (area under the curve, 0.842) and 80% (area under the curve, 0.889), respectively. The PFS rate of different groups and the predictive value using ΔSUV_{max} and $\Delta SUV_{max}\%$ are given in Table 3.

Kaplan-Meier estimates of PFS according to ΔSUV_{max} and $\Delta SUV_{max}\%$ are shown in Fig. 2, which reveals that the patients with higher ΔSUV_{max} and $\Delta SUV_{max}\%$ are of longer PFS. The PFS data are given in Table 4.

C. Prognostic significance of Ki67 positive index

With a 55% optimal cutoff value of Ki67 positive index calculated using ROC curve (Fig. 3), the PFSs are given in Table 4. The accuracy of Ki67 for predicting 2-year PFS is 80% (PPV = 77.8%, and NPV = 81.2%). Kaplan-Meier estimates based on Ki67 are shown in Fig. 4, which indicates that Ki67>55% can be an indicator to shorter PFS ($p = 0.019$).

D. Prognostic significance of ΔSUV_{max} associated with Ki67

Both the ΔSUV_{max} and Ki67 data were collected from 20 patients. From the results above, the prognostic value of both

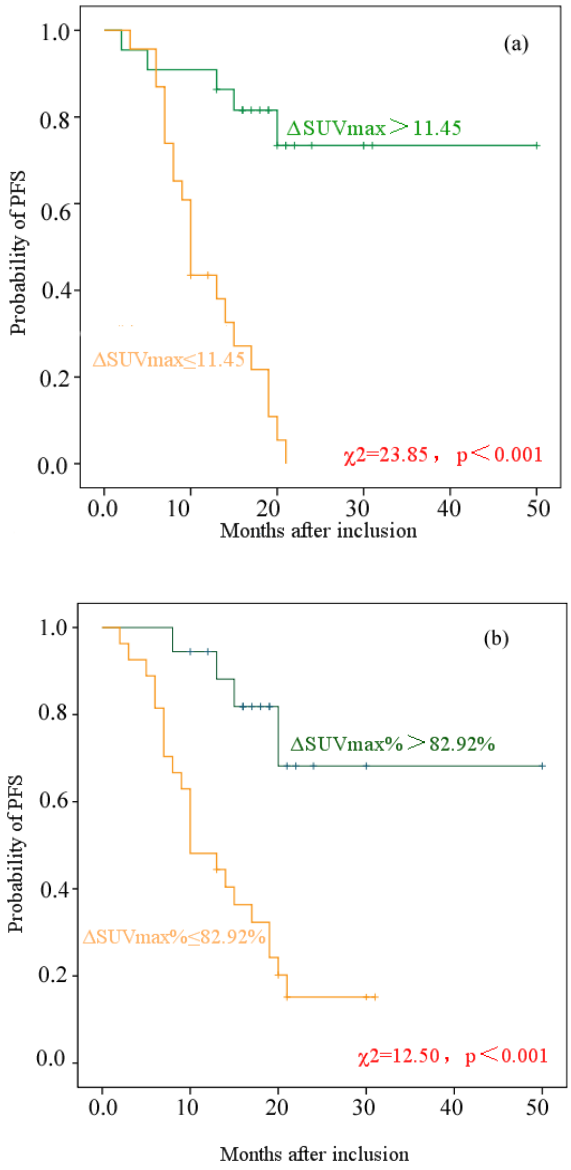

Fig. 2. (Color online) Kaplan-Meier estimates of PFS according to ΔSUV_{max} (a) and ΔSUV_{max}% (b).Patients with ΔSUV_{max} >11.45 and ΔSUV_{max} >82.92% were revealed to be of longer PFS.

ΔSUV_{max} and Ki67 for PFS were confirmed. Assuming an integrative score system as $\Delta SUV_{max} \leq 11.45$ and Ki67>55% being indicators to poor outcome ("negative" for predicting PFS) with a score of 1 point, the scores and outcomes are given in Table 5. The PFS is 100% (5/5) in patients scored 0 point ("double positive"), but 0% (0/7) in patients scored 2 points ("double negative"). That means, for predicting PFS, the PPV of 0 score group and the NPV of 2 score group are both as high as 100%. The accordance of ΔSUV_{max} and Ki67 may confirm the prediction of patients' outcome. PFS estimates based on the integrative score system using Kaplan-Meier methods are shown in Fig 5.

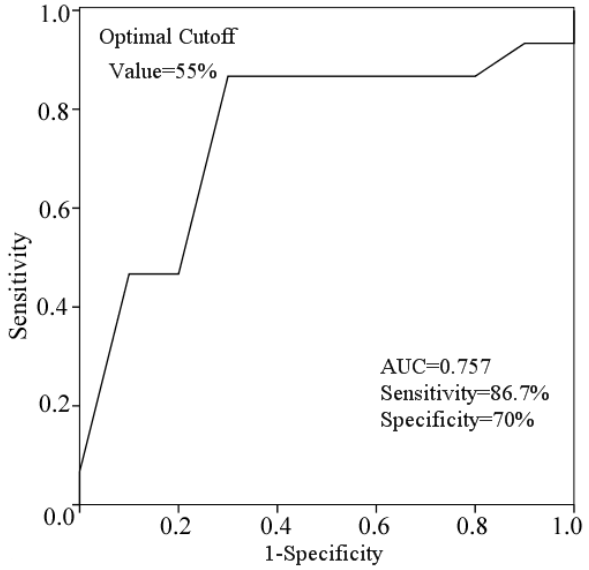

Fig. 3. ROC curve analysis of Ki67 positive index for PFS predicting, at the optimal cutoff value of 55%, sensitivity of 86.7% and specificity of 70%, with the accuracy being 80%.

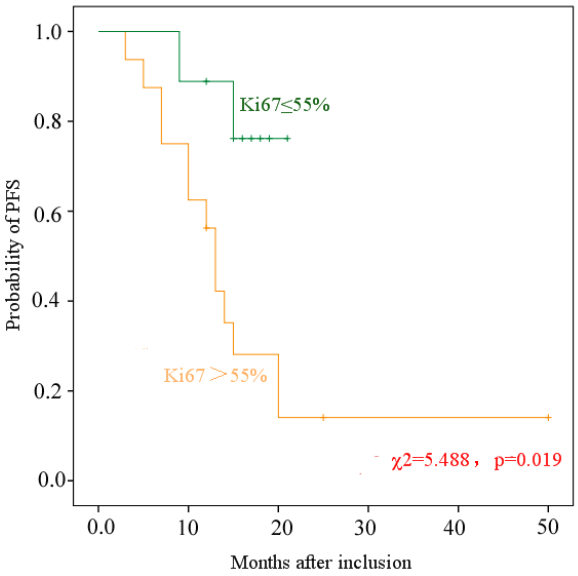

Fig. 4. (Color online) Kaplan-Meier estimates of PFS based on Ki67 with Ki67>55% being an indicator of shorter PFS ($\chi^2 = 5.488$, $p = 0.019$).

IV. DISCUSSIONS

Since 2007 when PET/CT was incorporated into the response evaluation criteria of NHL by the International Harmonization Project (IHP) in 2007 [1], the significance of PET/CT in NHL has been demonstrated. In a systematic review by Terasawa T *et al.* [10] on 19 studies that included 474 patients of Hodgkin disease and 254 NHL patients, the significance of PET/CT in identifying necrosis and residual

TABLE 5. Scores of ΔSUV_{max} associated with Ki67 positive index

Patients characteristics	Score	n	Events	2y-EFS	PPV[a]	NPV[b]
Total	/	20	13	65%	/	/
Ki67$\leq$55% and $\Delta SUV_{max} > 11.45$	0	5	0	100%	100%	/
Ki67 $>$ 55% and $\Delta SUV_{max} > 11.45$	1	8	6	25%	/	/
Ki67$\leq$55% and $\Delta SUV_{max} \leq 11.45$	1					
Ki67 $>$ 55% and $\Delta SUV_{max} \leq 11.45$	2	7	7	0%	/	100%

[a] PPV: positive predictive value of "0 score" for EFS.
[b] NPV: negative predictive value of "2 scores" for EFS.

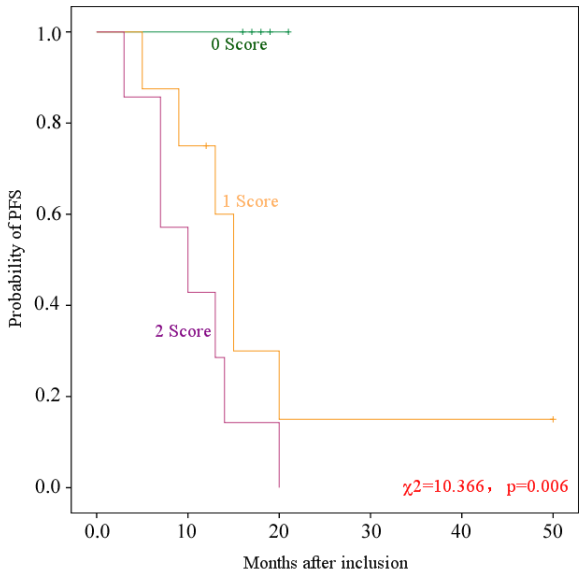

Fig. 5. (Color online) Kaplan-Meier estimates of PFS based on the integrative score system, revealing that the PFS tended to be shorter along with the scores getting higher ($\chi^2 = 10.366$, $p = 0.006$).

tumors after chemotherapy was confirmed. However, this is not enough for NHL management. In order to maintain remission and minimize side effect, it is necessary to assess the outcomes as early as possible. International prognostic index, which has been used for years, is a prognostic factor based on population. However, metabolic imaging such as PET/CT is of potential capacity for individual prognosis. In a study including 8 aggressive NHL patients, SUV_{max} decreased by 60% one week after the first dose of chemotherapy [11]. The potency of PET/CT for early prognosis was confirmed by this result. Nowadays, early (after 2 cycles of chemotherapy) and interim (after 4 cycles) PET/CT assessments are of concern in NHL [5, 12].

Since the accuracy of early or interim PET/CT for assessing patients' outcome was not high enough by just visual analysis according to various criteria [2, 3, 13], it is believed that the prognostic accuracy can be improved through SUV analysis [4]. SUV is a semi quantitative parameter measured in daily PET/CT scan, which has advantages such as non-invasive, easy to calculate and wide application. However, controversy exists because of its susceptibility to various factors. It is necessary to do something to minimize the influencing factors. In this study, all the acquisitions were performed on the same machine in the same institution, ensuring no influence of the machine type is caused. Scans were done 50–60 minutes after the tracer injection, which is considered as the duration required for the FDG uptake to reach a plateau, so the influence caused by imaging delay was minimized. And in order to decrease the partial-volume effect, SUV_{max} was chosen instead of SUV_{mean}. By controlling imaging conditions, SUV_{max} was repeatable [14].

However, SUV calculations are affected by a number of factors, which cannot be avoided totally. Therefore, SUV reduction based on the same machine, the same acquisition conditions and the same method of normalization might be more reliable. In studies including 92 DLBCL patients, the optimal cutoff values of SUV_{max} reduction after 2 and 4 cycles of chemotherapy were 65.7% and 72.9%, respectively [5, 12], with PPVs of 81.3% and 70.6% , and NPVs of 76.1% and 79.4%, respectively. These studies also pointed out that the prognostic value of SUV_{max} reduction analysis showed no significant difference after 2 cycles and after 4 cycles of therapy, through visual analysis did show a higher prognostic value after 4 cycles than that after 2 cycles. Similarly, the present study confirmed the significance of SUV_{max} reduction in DLBCL patients' prognosis, but due to the limit of patient number, the "interim PET/CT" was not restricted to be performed after 4 cycles (4 after 2 cycles and 1 after 3 cycles), which was a heterogeneity in this study.

Ki67 positive index is a marker of tumor cell proliferation, and high Ki67 means a risk factor in various malignant tumors [15–17], including lymphoma [6–9]. In a study including 58 DLBCL patients who accepted R-CHOP chemotherapy, Ki67 $>$ 80% was an indicator of shorter PFS and OS [18]. Shou *et al*. [19] revealed a positive correlation between Ki67 and FDG uptake in NHL, figuring out that the SUV_{ave} of the LCL (large cell lymphoma) group was significantly higher than that of the SCL (small cell lymphoma) with relatively little overlap between the groups.

Several groups suggested that by integrating SUV analysis with other clinical risk factors, the prognostic value might be improved. In Ref. [20], a parameter named "SIMaxSUV" was defined as SUV_{max} multiplied by the maximal diameter of the dominant lesion, and used as an independent prognostic factor for PFS. In Ref. [21], scores counted by integration of SUV_{max} reduction, age-adjusted IPI and molecular subtype of DLBCL used as significance in predicting OS.

In FDG PET/CT, the false positive results caused by inflammatory response after therapy can be the most important

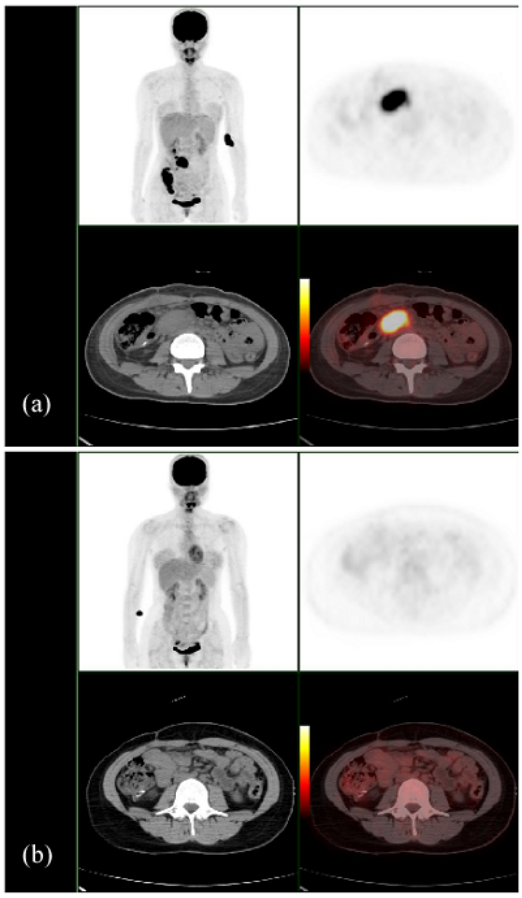

Fig. 6. (Color online) PET/CT images of a 29 years-old female, DLBCL stage IV, Ki67 of 50%. The initial scan found mesenteric lymph nodes and right colon involvement, SUV_{max} was 21.9(a), interim PET/CT found no apparent malignant lesion and SUV_{max} was 2.0(b), ΔSUV_{max} and $\Delta SUV_{max}\%$ were 19.9 and 90.9%, respectively. Integrative score was 0. Although the age-adjusted IPI was high, no symptom of progression or relapse was found during the follow-up of 26 months.

factor affecting the accuracy of prognosis. ^{18}F-FLT, which is an analogue of thymine, can reflect the cell proliferation level, and is confirmed to be a negative predictor of response correlating with the IPI scores [22]. FLT is known to be able to decrease the false positive results caused by inflammatory response, but it is not yet applied routinely in clinic. Fortunately, Ki67, which is widely used in clinical practice to reflect tumor proliferation, is also of significance for prognosis, as mentioned above.

An attempt was made in this study to evaluate the prognostic significance of the integration of interim SUV reduction and Ki67 positive index. However, no significant difference was found between the prognostic values of ΔSUV_{max} and $\Delta SUV_{max}\%$, with p values of 0.970 and 0.318, respectively, comparing with their PPVs and NPVs through two dimensional cross tables.

It was observed that the PPV of 0-score patients and NPV of 2-score patients were both as high as 100%. This score system integrated two important aspects of tumor biological behavior, glucose metabolism and tumor cell proliferation, which might be the feasibility for improving the prognostic capacity. Although the sample size was somewhat small, the accordance of these two parameters seemed to confirm the prognosis, especially in the 0-score group (Fig. 6), implying that low Ki67 could be helpful in selecting a subset of patients, for whom a high reduce of FDG uptake means a very good prognosis.

However, limited by the clinical practice, no data about Ki67 reduction was collected, which might be more associated with SUV_{max} reduction and more accurate for outcome predicting. On the other hand, potential clinical implications after interim PET/CT scan were not taken into consideration, which might somewhat affect patients' outcomes. Further efforts will be made in expanding the sample size and recording Ki67 after therapy. A perspective study to minimize the variety of SUVs and exclude the potential impact derived from therapeutic alteration, shall be devised.

V. CONCLUSION

In summary, ΔSUV_{max} and Ki67 positive index were both of significance in DLBCL prognosis. The prognostic accuracy may be confirmed when ΔSUV_{max} was in accordance with Ki67, especially in selecting patients with pretty good outcomes. Further perspective study with large sample shall be contributing.

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